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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

ATTY.'S DOCKET: SHALEV=2A

In re Application of:	)	Art Unit: 3762
	)	
Alon SHALEV et al.	)	Examiner:
	)	
Appln. No.: 10/753,882	)	Washington, D.C.
	)	
Filed: January 9, 2004	)	Confirmation No.
	)	
For: METHOD AND APPARATUS FOR STIMULATING THE...	)	May 13, 2004

Honorable Commissioner for Patents
U.S. Patent and Trademark Office
2011 South Clark Place
Crystal Plaza Two, Lobby, Room 1B03
Arlington, Virginia 22202

PETITION TO MAKE SPECIAL

Sir:

This is a petition pursuant to MPEP Section 708.02 VIII to accelerate examination of the above-referenced patent application. This petition is accompanied by the fee set forth in 37 C.F.R. Section 1.17(h).

The Applicant is filing a preliminary amendment of this application on even date herewith. It is believed that this application, as amended, presents only claims directed to a single invention. However, should the US Patent and Trademark Office determine that the present claims are not directed to a single invention, the Applicant will make an election without traverse. An International Search Report (ISR) was issued by the International Searching Authority (ISA/US) in International Application No. PCT/IL01/00402 (hereinbelow, the "PCT Application"), which is a counterpart of the present

application. The ISR did not indicate a lack of unity of invention. All of the claims that are currently pending in the present application, and which do not have counterparts in the PCT Application, are dependent claims that depend from independent claims with counterparts in the PCT Application. A copy of the ISR is attached as Exhibit A.

Detailed discussion of references

After entry of the Preliminary Amendment filed concurrently herewith, this application will contain claims 1, 3, 9-12, 17, 26, 29, 31, 37-41, 45-46, 54, 57-58, 67-76, 79-80, 131-140, 143-144 and 407-415, of which two independent and 51 dependent claims are currently pending. Claim 1 is an independent apparatus claim, and claim 29 is a parallel independent method claim. The specification of the present patent application is identical in content to that of the PCT Application. Claims 1 and 29 in the present application are identical to claims 1 and 32, respectively, in the PCT Application, as examined for the ISR.

The ISR lists the field of search in Section B as US classes 607/1, 2; 604/54; 424/434. In the ISR, Yee (US Patent 4,886,493) and Peyman (US Patent 5,855,907) are cited as "A" references relevant to claims 1-64 in the PCT Application, and Roberts (US Patent 4,152,928) and Colley et al. (US Patent 4,319,580) are cited as "X" references relevant to claims 65-72 in the PCT Application. Copies of these references were made of record in an Information Disclosure Statement submitted November 24, 2003 in parent application Serial No. 10/258,714. The present application does not include

claims equivalent to claims 65-72 in the PCT Application. Therefore, the '928 and '580 patents, which the ISR listed as relevant only to these claims, will not be discussed herein.

Claim 1 in the present patent application is drawn to apparatus for modifying a property of a brain of a subject, including one or more electrodes adapted to be applied to a sphenopalatine ganglion (SPG) of the patient or a neural tract originating in or leading to the SPG (together, hereinbelow, an "SPG-related site"), and a control unit adapted to drive the electrodes to apply a current to the SPG-related site capable of inducing an increase in permeability of a blood-brain barrier (BBB) of the patient. Claim 29 is a method claim parallel to claim 1.

Yee, identified in the ISR, describes an applicator and process for accomplishing SPG block by applying medication to the area of the SPG. Peyman, also identified in the ISR, describes a method for treating migraine headache including topical administration of a migraine-ameliorating effective amount of an opioid. As indicated in the ISR, neither Yee nor Peyman is of particular relevance to the claims of the present application. For example, neither describes the application of a current to an SPG-related site, as recited in claims 1 and 29.

The Applicant has submitted three Information Disclosure Statements, dated November 24, 2003, December 1, 2003, and April 14, 2004, respectively, in parent application Serial No. 10/258,714. Although the references in these Information Disclosure Statements, other than those

mentioned above, were not cited in the ISR, a discussion of these references is included hereinbelow, in order to expedite examination of the present application.

US Patent 6,405,079 to Ansarinia describes a method for electrically stimulating the sinuses and adjacent dura for treating various medical conditions. The '079 patent describes the application of anesthetic agents (such as lidocaine) to the SPG, but does not suggest the application of a current to an SPG-related site, as recited in claims 1 and 29. In addition, the '079 patent does not suggest increasing the permeability of the BBB, as recited in claims 1 and 29.

US Patent 6,526,318 to Ansarinia describes a method for electrically stimulating the SPG, sphenopalatine nerves, or vidian nerves for treating various medical conditions. The date of the '318 patent as a reference under 35 U.S.C. 102(e) is June 16, 2000, which is after the May 8, 2000 filing date of US Provisional Patent Application 60/203,172, from which the PCT Application and the present application claim priority. The Applicant's '172 provisional patent application, in turn, describes and claims stimulating the SPG to increase transport across the BBB. In any event, the Applicant believes that the '318 patent does not describe the invention claimed in claims 1 or 29 of the present patent application. For example, the '318 patent does not suggest increasing the permeability of the BBB, as recited in claims 1 and 29.

US Patent 5,031,618 to Mullett describes methods for electrically stimulating the spinal cord responsively to sensing a position of the patient. The '618 patent does not suggest the application of a current to an SPG-related site or increasing the permeability of the BBB, as recited in claims 1 and 29.

US Patent 5,938,690 to Law et al. describes a neuromodulation system for managing pain and/or various motor disorders. The '690 patent does not suggest the application of a current to an SPG-related site or increasing the permeability of the BBB, as recited in claims 1 and 29.

Delepine et al., in "Plasma protein extravasation induced in the rat dura mater by stimulation of the parasympathetic sphenopalatine ganglion," Experimental Neurology 147:389-400 (1997), describe electrical stimulation of the SPG to activate the intracranial parasympathetic system. Delepine et al. do not suggest increasing the permeability of the BBB, as recited in claims 1 and 29.

Hara H et al., in "Parasympathetic cerebrovascular innervation: an anterograde tracing from the sphenopalatine ganglion in the rat," Neurosurgery 32:822-827 (1993), describe the parasympathetic cerebrovascular innervation of the rat SPG, as explored by injecting horseradish peroxidase into the SPG and tracing anterogradely labeled nerve fibers. Hara et al. do not suggest increasing the permeability of the BBB, as recited in claims 1 and 29.

Ruskell GL, in "The orbital branches of the pterygopalatine ganglion and their relationship with internal carotid nerve branches in primates," J Anat 106:323-339 (1970), describes the anatomy of the orbital branches of the pterygopalatine ganglion (SPG), as studied in dissections of monkeys and humans. Ruskell does not suggest increasing the permeability of the BBB, as recited in claims 1 and 29.

Kroll RA et al., in "Outwitting the blood-brain barrier for therapeutic purposes: osmotic opening and other means," Neurosurgery 42:1083-1100 (1998), review clinical techniques for delivering therapeutic agents across the BBB. Techniques discussed include osmotic BBB disruption, pharmacological modification of the BBB with bradykinin, and direct intracerebral infusion. Kroll et al. do not suggest applying a current to an SPG-related site, as recited in claims 1 and 29.

Sanders M et al., in "Efficacy of sphenopalatine ganglion blockade in 66 patients suffering from cluster headache: a 12- to 70-month follow-up evaluation," Journal of Neurosurgery 87:876-880 (1997), report the results of a study of the effectiveness of radiofrequency lesions of the SPG in treating cluster headache in human patients. Sanders et al. do not suggest increasing the permeability of the BBB, as recited in claims 1 and 29.

Lee G et al., in "Drug transporters in the central nervous system: brain barriers and brain perenchyma considerations," Pharmacol Rev 53(4):569-596 (2001), review drug transport in the central nervous system, focusing on characteristics of several well-known membrane drug transporters.

SPG-related sites are not discussed in this review article, as recited in claims 1 and 29.

van de Waterbeemd H et al., in "Estimation of blood-brain barrier crossing of drugs using molecular size and shape, and H-bonding descriptors," Journal of Drug Targeting 6:151-165 (1998), describe the influence of physicochemical properties, including lipophilicity, H-bonding capacity, and molecular size and shape descriptors, on brain uptake of CNS drugs. van de Waterbeemd et al. do not suggest the application of a current to an SPG-related site or increasing the permeability of the BBB, as recited in claims 1 and 29.

Suzuki N et al., in "Selective electrical stimulation of postganglionic cerebrovascular parasympathetic nerve fibers originating from the sphenopalatine ganglion enhances cortical blood flow in the rat," Journal of Cerebral Blood Flow and Metabolism 10:383-391 (1990), report that electrical stimulation of postganglionic nerve fibers from the SPG induces an increase in ipsilateral cortical blood flow in the rat. Suzuki et al. do not suggest increasing the permeability of the BBB, as recited in claims 1 and 29.

Suzuki N et al., in "Effect on cortical blood flow of electrical stimulation of trigeminal cerebrovascular nerve fibers in the rat," Acta Physiol Scand 138:307-315 (1990), report experimental results in which electrical stimulation of the nasociliary nerve in the rat caused an increase in cortical blood flow. Suzuki et al. do not suggest increasing the permeability of the BBB, as recited in claims 1 and 29.

Samad TA et al., in a letter entitled "Interleukin-1beta-mediated induction of Cox-2 in the CNS contributes to inflammatory pain hypersensitivity," Nature 410:471-5 (March 2001), report that the prevention of central prostanoid production, by inhibiting the interleukin-1beta-mediated induction of Cox-2 in neurons or by inhibiting central Cox-2 activity, reduces centrally generated inflammatory pain hypersensitivity. The publication date of the Samad et al. letter is March 2001, which is after the May 8, 2000 filing date of US Provisional Patent Application 60/203,172, from which the PCT Application and the present application claim priority. In any event, the Applicant believes that Samad et al. do not describe the invention claimed in claims 1 or 29 of the present patent application. For example, Samad et al. do not suggest increasing the permeability of the BBB, as recited in claims 1 and 29.

Major DA et al., in "Odorants presented to the rat nasal cavity increase cortical blood flow," Chem. Senses 24:665-669 (1999), report that presenting certain odorants to the rat nasal cavity increases cortical blood flow. Major et al. do not suggest increasing the permeability of the BBB, as recited in claims 1 and 29.

Fusco BM et al., in "'Capsaicin-sensitive' sensory neurons in cluster headache: pathophysiological aspects and therapeutic indications," Headache 34:132-137 (1994), describe the effect of the application of capsaicin to the nasal mucosa of human cluster headache patients. They report that such application induced vasodilation in the internal carotid. Fusco

et al. do not suggest increasing the permeability of the BBB, as recited in claims 1 and 29.

Lambert GA et al., in "Decreased carotid arterial resistance in cats in response to trigeminal stimulation," Journal of Neurosurgery, 61:307-315 (1984), report experimental results in which stimulation of the trigeminal nerve or ganglion in the cat caused a frequency-dependent reduction in carotid vascular resistance, increasing carotid blood flow at higher frequencies. Lambert et al. do not suggest increasing the permeability of the BBB, as recited in claims 1 and 29.

Silver WL, in "Neural and pharmacological basis for nasal irritation," in Tucker WG et al. (eds.), Sources of Indoor Air Contaminants, Ann. NY Acad. Sci., 641:152-163 (1992), reviews the physiological responses of the trigeminal nerve in the nasal cavity to chemical stimuli. Silver does not suggest increasing the permeability of the BBB, as recited in claims 1 and 29.

Branston NM, in "The physiology of the cerebrovascular parasympathetic innervation," British Journal of Neurosurgery 9:319-329 (1995), reviews the physiology of parasympathetic fibers, including the SPG, that innervate the cerebral vessels. He describes experimental studies in animals in which electrical stimulation of parasympathetic fibers, including the SPG, increased cerebral blood flow. Branston does not suggest increasing the permeability of the BBB, as recited in claims 1 and 29.

Branston NM et al., in "Contribution of cerebrovascular parasympathetic and sensory innervation to the short-term control of blood flow

in rat cerebral cortex," J Cereb Blood Flow Metab 15(3):525-31 (1995), describe blocking the nasociliary nerve (NCN) or the NCN together with parasympathetic fibers from the SPG in rats. The blocking was performed using a cold probe, which the authors contrast with previous experiments using electrical stimulation of parasympathetic fibers. Branston et al. do not suggest increasing the permeability of the BBB, as recited in claims 1 and 29.

Toda N et al., in "Cerebral vasodilation induced by stimulation of the pterygopalatine ganglion and greater petrosal nerve in anesthetized monkeys," Neuroscience 96(2):393-398 (2000), describe electrical stimulation of the SPG and the greater petrosal nerve in monkeys, which resulted in vasodilation of ipsilateral cerebral arteries. Toda et al. do not suggest increasing the permeability of the BBB, as recited in claims 1 and 29.

Seylaz J et al., in "Effect of stimulation of the sphenopalatine ganglion on cortical blood flow in the rat," J Cereb Blood Flow Metab 8:875-8 (1988) report experimental results in the rat in which electrical stimulation of the SPG increased cerebral blood flow and tissue PO2 by about 50% and about 20%, respectively. Seylaz et al. do not suggest increasing the permeability of the BBB, as recited in claims 1 and 29.

Toda N et al., in "Preganglionic and postganglionic neurons responsible for cerebral vasodilation mediated by nitric oxide in anesthetized dogs," J Cereb Blood Flow Metab 20:700-708 (2000), report that electrical stimulation of the pterygopalatine ganglion (the SPG) caused vasodilation of

ipsilateral cerebral arteries in dogs. Toda et al. do not suggest increasing the permeability of the BBB, as recited in claims 1 and 29.

Young F, in "Electrical stimulation of the trigeminal nerve root for the treatment of chronic facial pain," J Neurosurg 83:72-78 (1995), describes the implantation of an electrical stimulating system, including a pulse generator and an electrode on the trigeminal nerve root, for treating chronic facial pain. Young does not suggest increasing the permeability of the BBB, as recited in claims 1 and 29.

The following articles describe the electrical stimulation of the vidian nerve in human patients suffering from chronic (hypertrophic) non-allergic rhinitis:

> Rucci L et al., "Histamine release from nasal mucosal mast cells in patients with chronic hypertrophic non-allergic rhinitis, after parasympathetic nerve stimulation," Agents Actions 25:314-20 (1988)
>
> Rucci L et al., "Effects of vidian nerve stimulation on the nasal and maxillary sinus mucosa," The Journal of Laryngology and Otology 98:597-607 (1984)
>
> Rucci L et al., "Vidian nerve resection in chronic hypertrophic non allergic rhinitis: effects on histamine content, number and rate of degranulation processes of mast cells in nasal mucosa," Rhinology 23:309-314 (1985)
>
> Rucci L et al., "Tympanometric variations induced by vidian nerve stimulation in humans," The Journal of Laryngology and Otology 99:355-358 (1985)
>
> Masini E et al., "Stimulation and resection of vidian nerve in patients with chronic hypertrophic non-allergic rhinitis: effect on histamine content in nasal mucosa," Agents and Actions 18:251-3 (1986)

These articles do not suggest increasing the permeability of the BBB, as recited in claims 1 and 29.

Suzuki N et al., in "Origins and pathways of cerebrovascular vasoactive intestinal polypeptide-positive nerves in rat," J Cereb Blood Flow Metab 8:697-712 (1988), describe denervation experiments and retrograde axonal tracing methods they performed for clarifying the origins and pathways of vasoactive intestinal polypeptide (VIP)-containing nerve fibers in the rat. Suzuki et al. do not suggest the application of a current to an SPG-related site or increasing the permeability of the BBB, as recited in claims 1 and 29.

The following patents and patent application publications to Levin describe compositions, apparatus, and methods for inhibiting cerebral neurovascular disorders and muscular headaches: US Patent 6,432,986, US Patent 6,491,940, US Patent Application Publication 2003/0133877, PCT Publication WO 99/03473, and PCT Publication WO 00/44432. The following patent applications to Levin additionally describe compositions, apparatus, and methods for inhibiting cephalic inflammation: US Patent Application Publication 2001/0004644 and PCT Publication WO 01/43733 (all seven of these publications together are hereinbelow referred to as the "Levin family of publications").

The Levin family of publications describes treatment techniques for inhibiting a cerebral neurovascular disorder, including anesthetizing a dorsonasal nerve structure, which is defined as the SPG or a nerve structure located in close anatomic proximity to the SPG. One technique described for anesthetizing a dorsonasal nerve structure is the application of electrical potential to a dorsonasal nerve structure (e.g., the '940 patent, col. 25, line 61).

Some of the Levin family of publications describe a dorsonasally implanted electronic neural stimulator for effecting nerve block of a dorsonasal nerve structure (e.g., the '940 patent, col. 53, lines 7-22). The Levin family of publications does not suggest increasing the permeability of the BBB, as recited in claims 1 and 29.

Bolay H et al., "Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model," Nature Medicine 8:136-142 (February 2002), was published after the May 8, 2000 filing date of US Provisional Patent Application 60/203,172, from which the PCT Application and the present application claim priority, and after the May 7, 2001 filing date of the PCT Application.

Conclusion

Accordingly, granting of this petition to make special is earnestly solicited.

Respectfully submitted,

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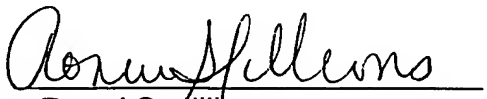
Attorneys for Applicant

By 
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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 November 2001 (15.11.2001)

PCT

(10) International Publication Number
WO 01/85094 A3

(51) International Patent Classification[7]: A61B 10/00

(21) International Application Number: PCT/IL01/00402

(22) International Filing Date: 7 May 2001 (07.05.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/203,172 8 May 2000 (08.05.2000) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

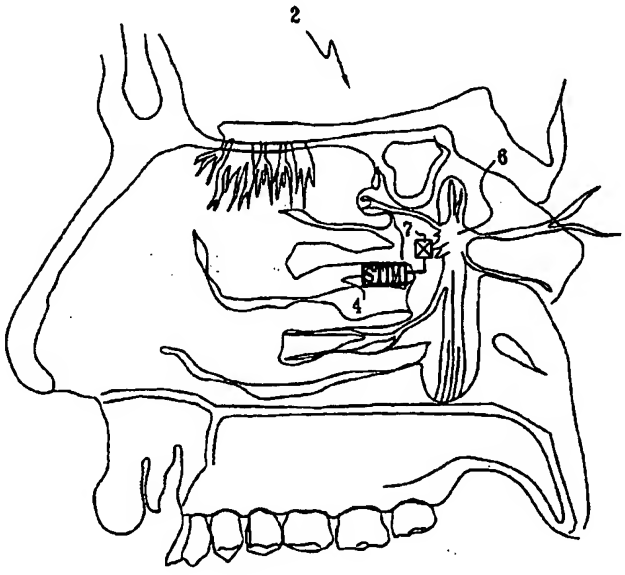
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
28 March 2002

[Continued on next page]

(54) Title: METHOD AND APPARATUS FOR STIMULATING THE SPHENOPALATINE GANGLION TO MODIFY PROPERTIES OF THE BBB AND CEREBRAL BLOOD FLOW



(57) Abstract: Apparatus for modifying a property of a brain of a patient is provided, including one or more electrodes (7), adapted to be applied to a site selected from a group of sites consisting of: a sphenopalatine ganglion (SPG) (6) of the patient and a neural tract originating in or leading to the SPG. A control unit (8) is adapted to drive the one or more electrodes to apply a current to the site capable of inducing (a) an increase in permeability of a blood-brain barrier (BBB) of the patient, (b) a change in cerebral blood flow of the patient, and/or (c) an inhibition of parasympathetic activity of the SPG.

WO 01/85094 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL01/00402

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61B 10/00
US CL : 607/2
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 607/1, 2; 604/54; 424/434

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,886,493 A (YEE) 12 December 1989, see abstract.	1-64
A	US 5,855,907 A (PEYMAN) 05 January 1999, see abstract.	1-64
X	US 4,152,928 A (ROBERTS) 08 May 1979, see entire document.	65-72
X	US 4,319,580 A (COLLEY et al.) 16 March 1982, see entire document.	65-72

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search
12 December 2001 (12.12.2001)

Date of mailing of the international search report
09 JAN 2002

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Form PCT/ISA/210 (second sheet) (July 1998)